## Tissue Force Programs Cell Fate and Tumor Aggression.

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**Public Summary:**
Forces experienced by cells and tissues can play a key role in directing the behavior of cells. Thus, when cells experience abnormal forces or other mechanical cues, or when cells respond inappropriately to normal mechanical cues, diseases such as cancer may develop. Further, mechanical stress and tissue stiffening can drive progression of disease by preventing drugs from reaching the diseased tissue and enhancing metastasis of cancer cells. It has also been shown that cancer cells that become more like stem cells may be more likely to metastasize and drive disease. Thus, in this review, we discuss the possibility that mechanical forces may promote disease by driving cancer cells to be more stem cell-like. We suggest that strategies to reduce the effects of mechanics in tumors may help prevent treatment-resistant cancers that metastasize.

**Scientific Abstract:**
Biomechanical and biochemical cues within a tissue collaborate across length scales to direct cell fate during development and are critical for the maintenance of tissue homeostasis. Loss of tensional homeostasis in a tissue not only accompanies malignancy but may also contribute to oncogenic transformation. High mechanical stress in solid tumors can impede drug delivery and may additionally drive tumor progression and promote metastasis. Mechanistically, biomechanical forces can drive tumor aggression by inducing a mesenchymal-like switch in transformed cells so that they attain tumor-initiating or stem-like cell properties. Given that cancer stem cells have been linked to metastasis and treatment resistance, this raises the intriguing possibility that the elevated tissue mechanics in tumors could promote their aggression by programming their phenotype toward that exhibited by a stem-like cell.Significance: Recent findings argue that mechanical stress and elevated mechanosignaling foster malignant transformation and metastasis. Prolonged corruption of tissue tension may drive tumor aggression by altering cell fate specification. Thus, strategies that could reduce tumor mechanics might comprise effective approaches to prevent the emergence of treatment-resilient metastatic cancers. Cancer Discov; 7(11); 1224-37. (c)2017 AACR.